WHAT IS CLAIMED IS:

1. A method of selecting a target polynucleotide, comprising:

(a) introducing into a population of host cells a library of insert polynucleotides; wherein at least one of said insert polynucleotides comprises the target polynucleotide; and wherein expression of said target polynucleotide directly or indirectly promotes host cell death;

(b) culturing said host cells; and

(c) collecting insert polynucleotides from those host cells which undergo cell death.

2. The method of claim 1, further comprising:

(d) introducing said collected polynucleotides into a population of host cells, wherein expression of said target polynucleotide directly or indirectly promotes host cell death;

(e) culturing said host cells; and

(f) collecting insert polynucleotides from those host cells which undergo cell death.

3. The method of claim 2, further comprising repeating steps (d)-(f) one or more times, thereby enriching for said target polynucleotide.

4. The method claim 3, further comprising purifying said collected polynucleotides.

5. The method of claim 1, wherein said cell death is the result of a cellular effect selected from the group consisting of cell lysis, expression of a

suicide gene product, a cytotoxic T-lymphocyte-induced lytic event, apoptosis, loss of viability, loss of membrane integrity, loss of structural stability, cell disruption, disruption of cytoskeletal elements, inability to maintain membrane potential, arrest of cell cycle, inability to generate energy, growth arrest, cytotoxic effects, cytostatic effects, genotoxic effects, and growth suppressive effects.

6. The method of claim 1, wherein said population of host cells is selected from the group consisting of: tumor cells, metastatic tumor cells, primary cells, transformed primary cells, immortalized primary cells, dividing cells, non dividing cells, terminally differentiated cells, pluripotent stem cells, committed progenitor cells, uncommitted stem cells, progenitor cells, muscle cells, epithelial cells, nervous system cells, circulatory system cells, respiratory system cells, endocrine cells, endocrine-associated cells, skeletal system cells, connective tissue cells, musculoskeletal cells, chondrocytes, osteoblasts, osteoclasts, myocytes, fully differentiated blood cells, fully differentiated epidermal cells, neurons, glial cells, kidney cells, liver cells, muscle cell progenitors, epithelial cell progenitors, nervous system cell progenitors, circulatory system cell progenitors, respiratory system cell progenitors, endocrine cell progenitors, endocrine-associated cell progenitors, skeletal system cell progenitors, connective tissue cell progenitors, musculoskeletal cell progenitors, chondrocyte progenitors, osteoblast progenitors, osteoclast progenitors, myocyte progenitors, blood cell progenitors, epidermal cell progenitors, neuron progenitors, glial cell progenitors, kidney cell progenitors, liver cell progenitors and any combination thereof.

7. The method of claim 1, wherein said host cells are adherent to a solid support.

8. The method of claim 7, wherein said solid support is selected from the group consisting of: tissue culture plastic, glass, polystyrene, polypropylene,

polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, magnetite, soluble material, partially soluble material, insoluble material, magnetic material, and nonmagnetic material.

9. The method of claim 7, wherein said solid support has a structure selected from the group consisting of: spherical, bead-like, bead, cylindrical, test tube-like, tube-like, tube, rod-like, rod, flat, sheet-like, sheet, test strip, strip-like, strip, bead, microbead, well, plate, tissue culture plate, petri plate, microplate, microtiter plate, flask, stick, vial, and paddle.

10. The method of claim 1, wherein said library of insert polynucleotides is selected from the group consisting of: a cDNA library, a genomic library, a combinatorial polynucleotide library, a library of natural polynucleotides, a library of artificial polynucleotides, a library of polynucleotides endogenous to said host cells, a library of polynucleotides exogenous to said host cells, an antisense library, and any combination thereof.

11. The method of claim 1, wherein expression of said target polynucleotide directly or indirectly promotes cell death upon exposure of said host cells to an agent.

12. The method of claim 11, wherein expression of said target polynucleotide indirectly promotes cell death upon exposure of said host cells to an agent.

13. The method of claim 11, wherein expression of said target polynucleotide directly promotes cell death upon exposure of said host cells to an agent.

14. The method of claim 11, wherein said agent is a member selected from the group consisting of: a physical agent, a chemical agent, and a biological agent.

15. The method of claim 11, wherein said physical agent is selected from the group consisting of: radiation, UV radiation, gamma radiation, infrared radiation, visible light, increased temperature, and decreased temperature.

16. The method of claim 11, wherein said chemical agent is selected from the group consisting of: a chemotherapeutic agent, a cytotoxic agent, and a DNA damaging agent.

17. The method of claim 11, wherein said biological agent is selected from the group consisting of: an antisense construct, an infectious agent, a therapeutic agent, an antibody, a cytotoxic T-lymphocyte (CTL), a ligand, a hapten, an epitope, and a receptor.

18. The method of claim 11, wherein said biological agent is selected from the group consisting of: an infectious agent, a therapeutic agent, an antibody, a ligand, a hapten, an epitope, and a receptor; and wherein said biological agent is conjugated to a toxin.

19. The method of claim 11, wherein said biological agent effects cell death by a process selected from the group consisting of: CTL-induced

cytotoxicity, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

20. The method of claim 11, wherein said biological agent comprises a cytotoxic T lymphocyte (CTL), wherein said CTL expresses surface CD4, wherein said target polynucleotide encodes a polypeptide, and wherein said polypeptide is processed and presented in association with a class II major histocompatibility molecule (MHC).

21. The method of claim 1, wherein expression of said target polynucleotide effects a cellular process selected from the group consisting of cellular differentiation, growth regulation, cellular proliferation, apoptosis, and hormonal response.

22. The method of claim 5, wherein said cell death is the result of apoptosis.

23. The method of claim 22, wherein apoptosis is induced through expression of a apoptosis-related gene product which directly promotes apoptosis.

24. The method of claim 22, wherein apoptosis is induced through expression of an apoptosis-related gene product which indirectly promotes apoptosis.

25. The method of claim 24, wherein said apoptosis-related gene product comprises a death domain containing receptor expressed on the surface of said host cells, and wherein said host cells are contacted with a ligand for said death domain containing receptor.

26. The method of claim 22, wherein said host cells are adherent to a solid support.

27. The method of claim 26, wherein those cells which have undergone apoptosis are released from said support.

28. The method of claim 27, wherein said released host cells, or contents thereof, are collected by removing the liquid medium in which said host cells are cultured.

29. The method of claim 26, wherein those host cells which have undergone apoptosis are fully or partially lysed, thereby releasing their cytoplasmic contents into the liquid medium in which said host cells are cultured.

30. The method of claim 29, wherein said released host cell contents are collected by removing the liquid medium in which said host cells are cultured.

31. The method of claim 5, wherein said cell death is the result of a cytotoxic T-lymphocyte-induced lytic event.

32. The method of claim 31, wherein said target polynucleotide encodes a target epitope for a cytotoxic T lymphocyte (CTL).

33. The method of claim 32, wherein said CTL is a CD4+ CTL.

34. The method of claim 32, wherein said target epitope is expressed on the surface of said host cells in the context of a native MHC molecule expressed

on said host cell, and wherein said host cells are contacted with CTLs which are restricted for said MHC molecule and specific for said target epitope.

35. The method of claim 34, wherein said MHC molecule is selected from the group consisting of a class I MHC molecule and a class II MHC molecule.

36. The method of claim 35, wherein said MHC molecule is a class II MHC molecule.

37. The method of claim 36, wherein said target polynucleotide is fused to a polynucleotide encoding Ii-80 fragment of the class II MHC molecule invariant chain.

38. The method of claim 31, wherein said host cells are adherent to a solid support.

39. The method of claim 38, wherein those cells which have undergone a CTL-mediated lytic event are released from said support.

40. The method of claim 39, wherein said released host cells, or contents thereof, are collected by removing the liquid medium in which said host cells are cultured.

41. The method of claim 38, wherein those host cells which have undergone a CTL-mediated lytic event are fully or partially lysed, thereby releasing their cytoplasmic contents into the liquid medium in which said host cells are cultured.

42. The method of claim 41, wherein said released host cell contents are collected by removing the liquid medium in which said host cells are cultured.

43. The method of claim 5, wherein said cell death is the result of expression of a suicide gene product.

44. The method of claim 43, wherein said suicide gene product is selected from the group consisting of a diphtheria toxin A chain polypeptide, a *Pseudomonas* exotoxin A chain polypeptide, a ricin A chain polypeptide, an abrin A chain polypeptide, a modeccin A chain polypeptide, and an alpha-sarcin polypeptide.

45. The method of claim 43, wherein said host cells are progenitor cells comprising a suicide gene operably associated with a tissue-restricted promoter; wherein expression of said target polynucleotide directly or indirectly induces transcription of said tissue-restricted promoter, resulting in expression of said suicide gene; and wherein expression of said suicide gene promotes death of those progenitor cells comprising said target polynucleotide.

46. The method of claim 45, wherein said host cell is a RAW cell, and wherein said suicide gene is operably associated with the TRAP promoter.

47. The method of claim 46, wherein said target polynucleotide directly or indirectly regulates osteoclast differentiation.

48. The method of claim 46, wherein said suicide gene encodes the Diphtheria toxin A subunit.

49. The method of claim 45, wherein said tissue-restricted promoter is identified by gene expression profiling of said host cells under different physical conditions in microarrays of ordered cDNA libraries.

50. The method of claim 49, wherein said expression profiling compares gene expression under different physical conditions in host cells infected with a eukaryotic virus expression vector, wherein said eukaryotic virus expression vector is the vector used to construct said library of polynucleotides.

51. The method of claim 43, wherein said host cells are non-dividing cells comprising a suicide gene operably associated with a proliferation-specific promoter; wherein expression of said target polynucleotide directly or indirectly induces transcription of said proliferation-specific promoter, resulting in expression of said suicide gene; and wherein expression of said suicide gene promotes death of those non-dividing host cells comprising said target polynucleotide.

52. The method of claim 51, wherein said proliferation-specific promoter is identified by gene expression profiling of said host cells under different physical conditions in microarrays of ordered cDNA libraries.

53. The method of claim 52, wherein said expression profiling compares gene expression under different physical conditions in host cells infected with a eukaryotic virus expression vector, wherein said eukaryotic virus expression vector is the vector used to construct said library of polynucleotides.

54. The method of claim 43, wherein said host cells are adherent to a solid support.

55. The method of claim 54, wherein those host cells expressing said suicide gene product are released from said support.

56. The method of claim 55, wherein said released host cells, or contents thereof, are collected by removing the liquid medium in which said host cells are cultured.

57. The method of claim 54, wherein those host cells expressing said suicide gene product are fully or partially lysed, thereby releasing their cytoplasmic contents into the liquid medium in which said host cells are cultured.

58. The method of claim 57, wherein said released host cell contents are collected by removing the liquid medium in which said host cells are cultured.

59. The method claim 5, wherein cell death occurs within a period selected from the group consisting of: 48 hours after expression of said insert polynucleotide, 24 hours after expression of said insert polynucleotide, and 12 hours after expression of said insert polynucleotide.

60. The method of claim 1, wherein said library of polynucleotides is constructed in a eukaryotic virus vector.

61. The method of claim 60, wherein said host cells are infected with said library at an MOI selected from the group consisting of: from about 1 to about 10, about 1 to about 5, and about 1.

62. The method of claim 60, wherein said eukaryotic virus vector is an animal virus vector.

63. The method of claim 60, wherein said eukaryotic virus vector is a plant virus vector.

64. The method of any one of claims 60, wherein said eukaryotic virus vector is capable of producing infectious viral particles in cells selected from the group consisting of insect cells, plant cells, and mammalian cells.

65. The method of claim 64, wherein said eukaryotic virus vector is attenuated.

66. The method of claim 64, wherein said eukaryotic virus vector is capable of producing infectious viral particles in mammalian cells.

67. The method of claim 65, wherein said attenuation is by genetic mutation.

68. The method of claim 65, wherein said attenuation is by reversible inhibition of virus replication.

69. The method of claim 60, wherein the naturally-occurring genome of said eukaryotic virus vector is DNA.

70. The method of claim 69, wherein the naturally-occurring genome of said eukaryotic virus vector is linear, double-stranded DNA.

71. The method of claim 70, wherein said eukaryotic virus vector is selected from the group consisting of an adenovirus vector, a herpesvirus vector and a poxvirus vector.

72. The method of claim 71, wherein said eukaryotic virus vector is a poxvirus vector.

73. The method of claim 72, wherein said poxvirus vector is selected from the group consisting of an orthopoxvirus vector, an avipoxvirus vector, a capripoxvirus vector, a leporipoxvirus vector, and a suipoxvirus vector.

74. The method of claim 73, wherein said poxvirus vector is an orthopoxvirus vector selected from the group consisting of a vaccinia virus vector and a raccoon poxvirus vector.

75. The method of claim 74, wherein said orthopoxvirus vector is a vaccinia virus vector.

76. The method of claim 74, wherein said host cells are permissive for the production of infectious viral particles of said virus.

77. The method of claim 75, wherein said vaccinia virus is attenuated.

78. The method of claim 77, wherein said attenuation is by genetic mutation.

79. The method of claim 77, wherein said attenuation is by reversible inhibition of virus replication.

80. The method of claim 77, wherein said vaccinia virus vector is derived from strain MVA.

81. The method of claim 77, wherein said vaccinia virus vector is derived from strain D4R.

82. The method of claim 72, wherein said insert polynucleotide is in operably associated with a transcriptional control sequence.

83. The method of claim 82, wherein said transcriptional control sequence functions in the cytoplasm of a poxvirus-infected cell.

84. The method of claim 82, wherein said transcriptional control sequence comprises a promoter.

85. The method of claim 84, wherein said promoter is constitutive.

86. The method of claim 85, wherein said promoter is a vaccinia virus p7.5 promoter.

87. The method of claim 85, wherein said promoter is a synthetic early/late promoter.

88. The method of claim 82, wherein said transcriptional control sequence comprises a transcriptional termination region.

89. The method of claim 60, wherein said library of insert polynucleotides is constructed in said eukaryotic virus vector by a method comprising:

(a) providing host cells comprising a linear DNA virus genome which has been cleaved to produce a first viral fragment and a second viral fragment, wherein said first fragment is nonhomologous with said second fragment;

(b) providing a population of transfer plasmids comprising said insert polynucleotides in operable association with a vector transcriptional control region, a 5' flanking region, and a 3' flanking region; wherein said 5' flanking region is homologous to said first viral fragment and said 3' flanking region is homologous to said second viral fragment; and wherein said transfer plasmids are capable of homologous recombination with said first and second viral fragments such that a viable virus genome is formed;

(c) introducing said transfer plasmids into said host cells under conditions wherein a transfer plasmid and said first and second viral fragments undergo *in vivo* homologous recombination, thereby producing a viable modified virus genome comprising an insert polynucleotide; and

(d) collecting said modified virus genome.

90. The method of claim 89, wherein said first and second viral fragments are produced by infecting said host cells with a virus comprising said linear DNA virus genome, and wherein said virus genome is cleaved *in vivo*.

91. The method of claim 89, wherein said first and second viral fragments are produced by cleaving an isolated linear DNA virus genome *in vitro*, and wherein said first and second viral fragments are introduced into said host cells.

92. The method of claim 91, wherein said virus genome comprises a first recognition site for a first restriction endonuclease; and wherein said first and second viral fragments are produced by digesting said viral genome with said first restriction endonuclease, and isolating said first and second viral fragments.

93. The method of claim 92, wherein said virus genome further comprises a second recognition site for a second restriction endonuclease; and wherein said first and second viral fragments are produced by digesting said viral genome with said first restriction endonuclease and said second restriction endonuclease, and isolating said first and second viral fragments.

94. The method of claim 93, wherein said first and second recognition sites are physically arranged in said genome such that the region extending between said first and second viral fragments is not essential for virus infectivity.

95. The method of claim 89, wherein said modified virus genome is packaged in an infectious viral particle.

96. The method of claim 89, wherein said modified virus genome is defective in an essential gene and said host cell comprises a complementing copy of said essential gene.

97. The method of claim 96, wherein said complementing copy of said essential gene is operably associated with an inducible promoter.

98. The method of claim 97, wherein said inducible promoter is selected from the group consisting of: a differentiation-induced promoter, a cell type-restricted promoter, a tissue-restricted promoter, a temporally-regulated promoter, a spatially-regulated promoter, a proliferation-induced promoter, a cell-cycle specific promoter.

99. The method of claim 89, wherein said linear DNA virus genome is a herpes virus genome.

100. The method of claim 89, wherein said linear DNA virus genome is an adenovirus genome.

101. The method of claim 89, wherein said linear DNA virus genome is a poxvirus genome.

102. The method of claim 101, wherein said poxvirus genome is a vaccinia virus genome.

103. The method of claim 96, wherein said linear DNA virus genome is a pox virus genome, and wherein said essential gene encodes uracil DNA glycosylase.

104. The method of claim 101, wherein said host cell further comprises a helper virus, and wherein said host cell is non-permissive for the production of infectious virus particles of said helper virus.

105. The method of claim 104, wherein said helper virus is an avipoxvirus.

106. The method of claim 105, wherein said helper virus is a fowlpox virus.

107. The method of claim 101, wherein the 5' and 3' flanking regions of said transfer plasmids are capable of homologous recombination with a vaccinia virus thymidine kinase gene.

108. The method of claim 107, wherein the 5' and 3' flanking regions of said transfer plasmids are capable of homologous recombination with a vaccinia virus HindIII J fragment.

109. The method of claim 107, wherein said transfer plasmid comprises an insert polynucleotide operably associated with a promoter selected from the group consisting of a vaccinia virus p7.5 promoter, a synthetic early/late promoter, and a vaccinia virus MH5 early/late promoter.

110. A method of selecting a target polynucleotide, comprising:

(a) introducing into a population of host cells a library of insert polynucleotides; wherein said library is constructed in a linear DNA virus vector; wherein at least one of said insert polynucleotides comprises said target polynucleotide; and wherein expression of said target polynucleotide directly or indirectly inhibits death of a host cell comprising said target polynucleotide;

(b) culturing said host cells; and

(c) collecting insert polynucleotides from those host cells which do not undergo cell death.

111. The method of claim 110, further comprising:

(d) introducing said collected polynucleotides into a population of host cells, and wherein expression of said target polynucleotide directly or indirectly inhibits death of a host cell comprising said target polynucleotide;

(e) culturing said host cells; and

(f) collecting insert polynucleotides from those host cells which do not undergo cell death.

112. The method of claim 111, further comprising repeating steps (d)-(f) one or more times, thereby enriching for said target polynucleotide.

113. The method of claim 112, further comprising purifying said collected polynucleotides.

114. A method of selecting a target polynucleotide, comprising:

(a) introducing into a population of host cells a library of insert polynucleotides; wherein said library is constructed in a linear DNA virus vector; wherein at least one of said insert polynucleotides comprises said target polynucleotide; wherein exposure of said host cells to an agent promotes cell death; and wherein expression of said target polynucleotide directly or indirectly inhibits death of a host cell comprising said target polynucleotide;

(b) culturing said host cells;

(c) exposing said host cells to said agent; and

(d) collecting insert polynucleotides from those host cells which do not undergo cell death.

115. The method of claim 114, further comprising:

(e) introducing said collected polynucleotides into a population of host cells, wherein exposure of said host cells to an agent promotes cell death; and wherein expression of said target polynucleotide directly or indirectly inhibits death of a host cell comprising said target polynucleotide;

(f) culturing said host cells;

(g) exposing said host cells to said agent; and

(h) collecting insert polynucleotides from those host cells which do not undergo cell death.

116. The method of claim 115, further comprising repeating steps (e)-(h) one or more times, thereby enriching for said target polynucleotide.

117. The method of claim 116, further comprising purifying said collected polynucleotides.

118. A method of selecting a target polynucleotide, comprising:

(a) introducing into a population of host cells a library of insert polynucleotides; wherein said library is constructed in a linear DNA virus vector; wherein at least one of said insert polynucleotides comprises the target polynucleotide; and wherein expression of said target polynucleotide directly or indirectly alters a phenotype of a host cell comprising said target polynucleotide;

(b) culturing said host cells; and

(c) collecting insert polynucleotides from those host cells which exhibit said altered phenotype.

119. The method of claim 118, further comprising:

(d) introducing said collected polynucleotides into a population of host cells, and wherein expression of said target polynucleotide directly or indirectly alters a phenotype of a host cell comprising said target polynucleotide;

(e) culturing said host cells; and

(f) collecting insert polynucleotides from those host cells which exhibit said altered phenotype.

120. The method of claim 119, further comprising repeating steps (d)-(f) one or more times, thereby enriching for said target polynucleotide.

121. The method of claim 120, further comprising purifying said collected polynucleotides.

122. The method of claim 118, wherein said altered phenotype is the expression of a reporter gene product.

123. The method of claim 122, wherein said reporter gene product is selected from the group consisting of an epitope, chloramphenicol acetyl transferase (CAT), green fluorescent protein (GFP), blue fluorescent protein (BFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), luciferase and β-galactosidase.

124. The method of claim 122, wherein expression of said target polynucleotide indirectly promotes expression of said reporter gene product in said host cells upon exposure of said host cells to an agent.

125. The method of claim 124, wherein said agent is selected from the group consisting of: an infectious agent, a therapeutic agent, an antibody, a ligand, a hapten, an epitope, and a receptor; and wherein said agent is labeled.

126. The method of claim 124, wherein said target polynucleotide encodes a secreted product.

127. A method of selecting a target polynucleotide encoding a secreted product, comprising:

(a) dividing host cells comprising a library of insert polynucleotides into pools; wherein said library is constructed in a linear DNA virus vector; wherein at least one of said insert polynucleotides comprises the target polynucleotide; and wherein expression of said target polynucleotide and secretion of said secreted product directly or indirectly alters a phenotype of an indicator cell;

(b) culturing said host cell pools in the presence of indicator cells;

(c) collecting insert polynucleotides from those host cell pools in which said indicator cells exhibit an altered phenotype.

128. The method of claim 127, further comprising:

(d) introducing said collected polynucleotides into host cells;

(e) dividing the host cells of (d) into pools; wherein expression of said target polynucleotide directly or indirectly alters a phenotype of said indicator cells;

(f) culturing said host cell pools in the presence of indicator cells;

(g) collecting insert polynucleotides from those host cell pools in which said indicator cells exhibit an altered phenotype.

129. The method of claim 128, further comprising repeating steps (d)-(g) one or more times, thereby enriching for said target polynucleotide.

130. The method claim 129, further comprising purifying said collected polynucleotides.

131. The method of claim 127, wherein said altered phenotype is the expression of a reporter gene product.

132. The method of claim 131, wherein said reporter gene product is selected from the group consisting of an epitope, chloramphenicol acetyl transferase (CAT), green fluorescent protein (GFP), blue fluorescent protein (BFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), luciferase and β-galactosidase.

133. The method of claim 127, wherein said target polynucleotide alters a phenotype of said indicator cells upon exposure of said host cells to an agent.

134. The method of claim 127, wherein expression of said target polynucleotide effects a cellular process selected from the group consisting of cellular differentiation, growth regulation, cellular proliferation, apoptosis, and hormonal response.

135. The method of claim 127, wherein said indicator cells are progenitor cells comprising a selectable gene product operably associated with a tissue-restricted promoter; wherein expression of said target polynucleotide directly or indirectly induces transcription of said tissue-restricted promoter, resulting in expression of said selectable gene product.

136. The method of claim 135, wherein said indicator cell is a RAW cell, and wherein the marker gene is operably associated with the TRAP promoter.

137. The method of claim 136, wherein said target polynucleotide directly or indirectly regulates osteoclast differentiation in said indicator cells.